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## Note

# A detailed study of the acetalation of D-mannitol with acetone–sulfuric acid*

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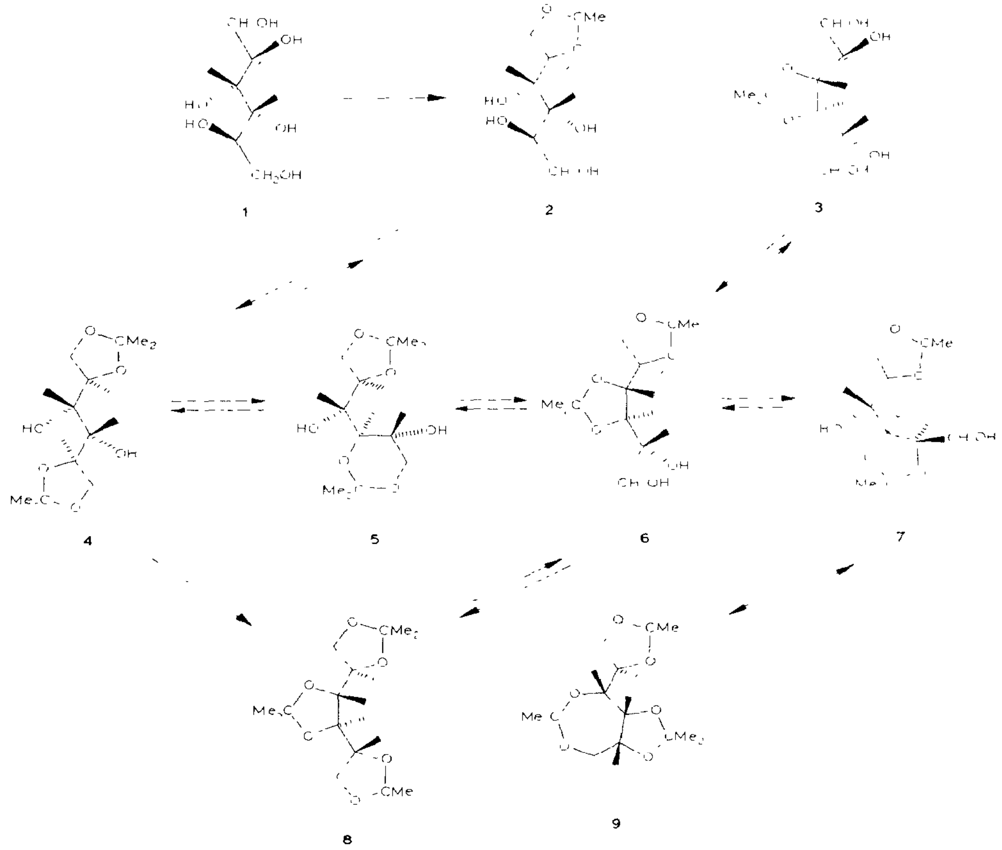
Recently, the formation of 1,2:3,6:4,5-tri-*O*-isopropylidene-D-mannitol (**9**) as a byproduct in the synthesis of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**4**) was described[2]. Because **9** is more sensitive towards acid-catalyzed hydrolysis than the isomeric 1,2:3,4:5,6-triacetal **8**, it was presumed that, under strongly acidic condi-



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*The acetalation of D-mannitol, Part III. For Part II, see ref 1.

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tions — generally used for the synthesis of triacetal **8** — isomer **9** is probably formed to a lesser degree and that it was not, therefore, detected previously. For proving this hypothesis, the reaction of D-mannitol with acetone in the presence of sulfuric acid[3] was investigated in detail *via* monitoring it by g.l.c.

## EXPERIMENTAL

*Acetalation of* D-*mannitol with acetone in the presence of sulfuric acid.* — The method described by Wiggins[3] for the synthesis of triacetal **8** was investigated in the following way. Parallel runs were quenched at different time-intervals by addition of triethylamine, and the composition of each run was analyzed, after acetylation, by g.l.c. As may be seen in Fig. 1 and Table I, the reaction yields a mixture

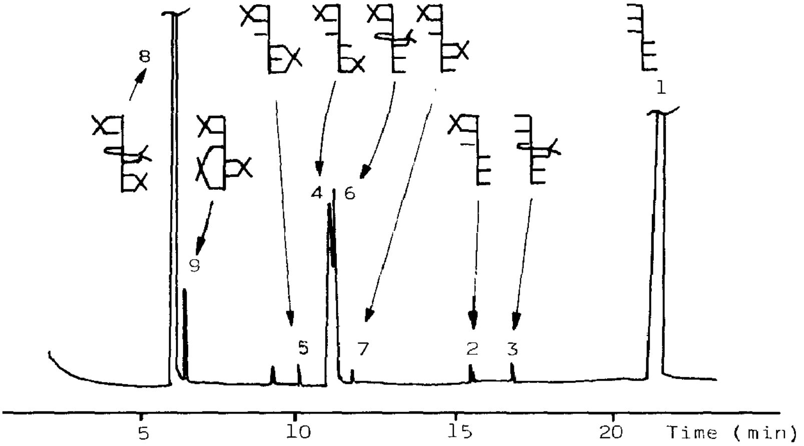

Fig. 1. G.l.c. of the acetylated reaction mixture obtained from D-mannitol and acetone in the presence of sulfuric acid after 2 h at 20°.

TABLE I

RELATIVE INTENSITIES (%) OF G L C PEAKS OBTAINED AFTER ACETYLATION OF THE REACTION MIXTURE OF D-MANNITOL WITH ACETONE IN THE PRESENCE OF SULFURIC ACID

| *Reaction time (h)* | *Peaks*[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 0.25 | 80 | + | + | 6 | + | 2 | + | 12 | |
| 0.50 | 67 | 0.2 | + | 8 | + | 3.5 | 0.3 | 20 | 0.8 |
| 1 | 44 | 0.6 | 0.5 | 12.5 | 0.8 | 5.0 | 0.4 | 35 | 1.0 |
| 2 | 22 | 1.1 | 1.3 | 12.0 | 0.9 | 11.0 | 0.4 | 50 | 1.2 |
| 3 | 11 | 1.0 | 2.2 | 8.5 | 1.1 | 19.0 | 0.4 | 56 | 1.0 |
| 5 | 5 | 1.1 | 2.4 | 7.0 | 1.0 | 21.0 | 0.4 | 60 | 1.2 |
| 7 | 3 | 1.1 | 2.6 | 7.5 | 1.0 | 21.5 | 0.4 | 61 | 1.0 |
| 16 | + | 1.0 | 2.8 | 8.0 | 0.9 | 23.0 | 0.4 | 63 | 0.9 |
| 24 | — | 1.0 | 2.7 | 8.0 | 0.9 | 23.0 | 0.4 | 63 | 1.0 |

[a] Peaks detectable, but with intensities of <0.2%, are marked with +.

of different mono-, di-, and tri-acetals, and an equilibrium is reached after 16 h, the mixture containing, besides triacetal **8** (63%), not only a small proportion of the corresponding isomer **9** (0.9%), but a substantial proportion of the isomeric 1,3:5,6- (**4**; 8%) and 1,2:3,4-diacetals (**6**; 23%), traces of the 1,2:4,6- (**5**) and 1,2:4,5-diacetals (**7**), as well as the 1,2- (**2**) and 3,4-monoacetals (**3**).

This rather unexpected result could be explained by analyzing the time-dependent isomer distribution of the reaction (see Table I). It may be seen that, in the beginning, formation of the 1,2-monoacetal (**2**), the 1,2:5,6-diacetal (**4**), and the 1,2:3,4:5,6-triacetal (**8**) is the dominating process, but hydrolysis of **8** also takes place, affording the 1,2:3,4-diacetal (**6**) and the 3,4-monoacetal (**3**). After 16 h, when a thermodynamically controlled equilibrium is reached, the two diacetals **6** and **4** are present in the ratio of ~3:1. Under the same conditions, the ratio of the isomeric triacetals **8** and **9** is ~65:1. Triacetal **9** is probably formed *via* diacetal **7**, which is always present in traces. As the ratio of some of the minor components (**2**, **5**, **6**, and **9**) was not significantly changed during the reaction, their participation in the equilibrium had to be proved by an independent approach.

*Reaction of triacetal* **8** *under the conditions of acetalation.* — Triacetal **8**, prepared according to the method described[3], contained, according to g.l.c. investigations, 0.2% of triacetal **9**. For obtaining pure starting material this crude triacetal was submitted to sublimation, yielding **8** containing not even traces of **9**. This material was dissolved in acetone containing sulfuric acid in the same ratio as the acetalation mixture previously used, and three equivalents of water (calculated on triacetal **8**) were added. Aliquots of this solution were removed at different time-intervals, the reactions were quenched by addition of triethylamine, and, after acetylation, the mixtures were analyzed by g.l.c.

From the results, listed in Table II, it may be seen that the partial hydrolysis

TABLE II

RELATIVE INTENSITIES (%) OF G.L.C. PEAKS OBTAINED AFTER ACETYLATION OF THE REACTION MIXTURE OF TRIACETAL **8** WITH ACETONE IN THE PRESENCE OF SULFURIC ACID AND WATER

| *Reaction time* | *Peaks*[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 | 3 | 4 | 5 | 6 | 8 | 9 |
| 5 min | + | 1.5 | 1.4 | — | 18.1 | 79 | — |
| 10 | + | 1.4 | 2.3 | + | 18.3 | 78 | — |
| 15 | + | 1.6 | 3.2 | 0.2 | 18.2 | 77 | + |
| 30 | + | 1.4 | 3.9 | 0.3 | 17.9 | 76 | 0.2 |
| 45 | + | 1.2 | 4.8 | 0.5 | 17.7 | 74 | 0.5 |
| 1 h | + | 1.3 | 6.2 | 0.4 | 17.3 | 73 | 0.9 |
| 2 | + | 1.1 | 6.5 | 0.6 | 17.2 | 73 | 1.5 |
| 5 | + | 1.2 | 6.5 | 0.6 | 17.3 | 72 | 1.7 |
| 24 | + | 1.3 | 6.5 | 0.6 | 17.1 | 73 | 1.4 |

[a] Peaks detectable, but with intensities of <0.2%, are marked with +; compounds **1** and **7** could not be detected

TABLE III

RELATIVE INTENSITIES (%) OF G.L C PEAKS OBTAINED AFTER ACETYLATION OF THE REACTION MIXTURE OF D-MANNITOL WITH ACETONE IN THE PRESENCE OF SULFURIC ACID AND ACETIC ACID

| *Reaction time* | *Peaks*[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 10 min | 46 | + | 0.5 | 4.9 | + | 3.8 | + | 44 | 0.6 |
| 20 | 27 | 0.2 | 0.7 | 3.7 | + | 7.4 | + | 60 | 0.9 |
| 30 | 12 | + | 0.8 | 2.4 | + | 9.9 | + | 72 | 1.0 |
| 1 h | + | + | 1.4 | 0.7 | + | 11.6 | + | 86 | 1.1 |
| 2 | — | + | 1.4 | 0.5 | + | 10.0 | + | 87 | 1.3 |
| 3 | — | + | 1.6 | 0.2 | + | 12.1 | + | 85 | 1.1 |
| 5 | — | + | 1.9 | + | + | 11.9 | + | 85 | 1.1 |

[a]Peaks detectable, but with intensities of <0.2%, are marked with +.

of triacetal **8** to the 1,2:3,4-diacetal **6** and the 3,4-monoacetal **3** is a very fast process, as, after 5 min, a ratio of these acetals was obtained that was very close to the equilibrium concentration, which is reached in ~1 h; only the ratio of the isomeric 1,2:5,6- and 1,2:3,4-diacetals (**4** and **6**) is shifted significantly towards a preponderance of the former.

*Acetalation of* D-*mannitol with acetone in the presence of sulfuric acid and acetic acid.* — For the large-scale preparation of triacetal **8**, a modification of the original procedure[3] has been used for years in our laboratory, by employing a higher concentration of sulfuric acid and some acetic acid*. In this way, the solubility of D-mannitol — which is the rate-determining factor — could be substantially increased and, according to t.l.c., the reaction was complete in 2 h. This reaction has now been monitored by g.l.c. after quenching parallel runs with triethylamine and subsequent acetylation. From the results, summarized in Table III, it may be seen that the reaction reaches equilibrium in ~1 h, and that triacetal **8** is formed in a maximum yield of 87%. This somewhat higher yield, compared to that (63%) for the original procedure, is probably due to the higher proportion of acetone used in the reaction, thereby shifting the equilibrium towards the fully acetalated derivatives.

It is interesting that the ratio of the isomeric diacetals **4** and **6** is completely shifted towards the latter; consequently, the equilibrium** between these isomers depends strongly on the reaction conditions.

The difference in the two acetalation methods could also be proved in preparative runs, because *via* the original method[3], triacetal **8** could be separated in a

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*When the concentration of the sulfuric acid was increased ten-fold and no acetic acid was employed, the reaction was complete in 5 h, but the yield of **8** did not increase.

**The equilibrium between diacetals **4**, **5**, **6**, and **7** is probably reached by rearrangement reactions which can take place under acidic conditions[1].

yield of only 51%*, whereas the modified procedure gave a yield of 67%. The purity of the crude triacetals obtained was, within experimental error, identical (98.6%), with triacetal **9** (0.4%) and diacetal **6** (1%) as impurities. The yield of **8** could not be further increased by simultaneously employing in the reaction such drying agents as sodium sulfate.

## EXPERIMENTAL

*General methods.* — The conditions used for g.l.c. and n.m.r.-spectral measurements have been described[1]. For identification of peaks, samples of acetylated, authentic material were prepared as described in the literature: **2** (ref. 5), **4** and **5** (ref. 1), **7** (ref. 2), **8** (ref. 3), and **9** (ref. 2); the acetylation of **3** and **6** is described herein.

*The acetalation of* D-*mannitol with acetone in the presence of sulfuric acid*[3]. — To aliquots (5 mL) of a solution of sulfuric acid (0.4 mL) in acetone (50 mL) was added dry mannitol (0.4 g), and the slurries were stirred for 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 24 h at 20°. A clear solution was obtained after 16 h. The reactions were quenched by addition of triethylamine (3 mL) and acetic anhydride (2 mL). After being kept overnight at room temperature, each mixture was diluted with chloroform and submitted to g.l.c. analysis. The results are listed in Table I.

*The acetalation of* D-*mannitol with acetone in the presence of sulfuric acid and acetic acid.* — To aliquots (4.3 mL) of a solution of sulfuric acid (2 mL) and acetic acid (1 mL) in acetone (40 mL) was added dry D-mannitol (0.2 g), and the slurries were stirred for 10, 20, and 30 min, and 1, 2, 3, and 5 h at 20°. Clear solutions were obtained after 45 min. The reactions were quenched by addition of triethylamine (3 mL) and acetic anhydride (2 mL). After being kept overnight at room temperature, each mixture was diluted with chloroform and submitted to g.l.c. analysis. The results are listed in Table III.

*Reaction of triacetal* **8** *with acetone in the presence of sulfuric acid and water.* — A solution of sulfuric acid (0.4 mL) in acetone (40 mL) and water (1 mL) was cooled to 20°, and a solution of pure triacetal **8** (6 g) in acetone (10 mL) was added. Aliquots (5 mL) were removed after 5, 10, 30, and 45 min, and 1, 2, 5, and 24 h. Triethylamine (3 mL) and acetic anhydride (2 mL) were successively added, and, after standing overnight at room temperature, each mixture was diluted with chloroform and submitted to g.l.c. analysis. The results are listed in Table II.

*Acetylation of* **3**. — A solution of monoacetal **3** (ref. 7) (2.2 g) in pyridine (10 mL) and acetic anhydride (6 mL) was kept overnight at room temperature to give, after the usual processing, 1,2,5,6-tetra-*O*-acetyl-3,4-*O*-isopropylidene-D-mannitol as a colorless syrup; $[\alpha]_D^{20}$ +49° (*c* 1, chloroform); $^1$H-n.m.r. data: $\delta$ 5.13 (m, H-2,5), 4.45 (dd, $J_{1,2} = J_{5,6} = 3$, $J_{1,1'} = J_{6,6'} = 10$ Hz, H-1,6), 4.10 (dd, $J_{1',2} = J_{6',5} = 6$ Hz, H-1',6'), 4.06 (m, H-3,4), 2.12 and 2.05 (2 acetyl-Me), and 1.43 (isopropylidene-Me).

*Anal.* Calc. for $C_{17}H_{26}O_{10}$: C, 52.30; H, 6.71. Found: C, 52.17; H, 6.80.

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*A similar yield of 53% was obtained by Stern and Wasserman[4], on repeating Wiggins's method[3]

*Acetylation of* **6**. — A solution of diacetal **6** (ref. 3) (1.3 g) in pyridine (5 mL) and acetic anhydride (2.5 mL) was kept overnight at room temperature, to give, after the usual processing, crude 5,6-di-*O*-acetyl-1,2:3,4-*O*-di-isopropylidene-D-mannitol, which was recrystallized from methanol–water (yield, 1.15 g, 66.5%); m.p. 61–63°, $[\alpha]_D^{20}$ +30.4° (*c* 1, chloroform); $^1$H-n.m.r. data: $\delta$ 5.2 (m, H-5), 4.33 (dd, $J_{5,6}$ = 3, $J_{6,6'}$ = 12 Hz, H-6), 4.2–3.7 (m, H-1,2,3,4,6′), 2.04 and 2.00 (2 acetyl-Me) and 1.38, 1.35, and 1.32 (isopropylidene-Me).

*Anal.* Calc. for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.32; H, 7.40.

*1,2:3,4:5,6-Tri-O-isopropylidene-*D*-mannitol* (**8**). — *Method a* (ref. 3). To a stirred solution of sulfuric acid (2 mL) in acetone (250 mL) was added dry D-mannitol (20 g), and stirring was continued for 16 h at room temperature. The clear solution was poured into a vigorously stirred (ultra-turax mixer), and extensively cooled, suspension of sodium carbonate (15 g) in ice–water (25 mL). Stirring was continued until the slurry became neutral (10 min), and then the precipitated salts were filtered off, and washed with acetone (50 mL). The filtrate and washings were combined and evaporated, and the semisolid residue was filtered with the aid of water, to yield crude **8** (17 g, 51.2%), m.p. 68–70°. A sample was treated with acetic anhydride–pyridine, and the products submitted to g.l.c. analysis, yielding the following results: **8** (98.6%), **9** (0.4%), and the diacetate of **6** (1%).

Completely pure **8** was obtained on sublimation at 2.700 kPa and 100° (bath temperature); m.p. 70–71°, $[\alpha]_D^{20}$ +14.7° (*c* 1, ethanol), +13.8° (*c* 1, chloroform); lit.[3] m.p. 69–70°, $[\alpha]_D^{20}$ +12.5° (*c* 9.6, ethanol); lit.[8] m.p. 67.5–68.5°, $[\alpha]_D^{20}$ +10.2° (*c* 2, ethanol).

*Method b.* — A slurry of dry D-mannitol (20 g) in acetone (400 mL) containing sulfuric acid (20 mL) and acetic acid (10 mL) was stirred for 1.5 h at room temperature. The clear solution obtained was processed as described in method *a*, using a suspension of sodium carbonate (150 g) in ice–water (250 mL) for neutralization. The resulting crude **8** (22.2 g, 66.9%), m.p. 68–70°, on g.l.c. investigation, gave, within the experimental error, results identical to those for method *a*.

When the reaction was carried out in the presence of sodium sulfate (20 g), crude **8** (22.6 g, 68.1%) was obtained.

## ACKNOWLEDGMENT

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